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## **Methylaminolaevulinic acid photodynamic therapy in the treatment of erythroplasia of Queyrat**

Feldmeyer, L ; Krausz-Enderlin, V ; Töndury, B ; Hafner, J ; French, L E ; Hofbauer, G F L

**Abstract:** **BACKGROUND:** Erythroplasia of Queyrat (EQ) is an intra-epithelial carcinoma of the penis. Progression to invasive carcinoma may occur. Its cause is unknown but some evidence suggests infection with human papillomavirus in the pathogenesis of EQ; however, recent data do not confirm this. Therapy is difficult and associated with important recurrence rates. Photodynamic therapy (PDT) employs a photosensitizer excited by visible light. The resulting photodynamic reaction selectively destroys atypical cells. Only few reports exist on the use of topical PDT in the treatment of EQ. **OBJECTIVE:** We report 11 cases of EQ treated by topical methylaminolaevulinic acid (MAL) PDT. **RESULTS:** Out of 11 male patients with EQ treated by topical MAL-PDT, 3 achieved complete remission sustained for 24 and 51 months and 4 a partial remission sustained for 2-45 months with a follow-up period of 4-45 months (1 patient lost to follow-up); surprisingly, 2 of the 4 patients with partial remission presented a complete remission after 20 and 45 months of follow-up, respectively, without further therapy. Four patients showed progression of the disease. **CONCLUSION:** Whereas topical MAL-PDT offers the advantages of tumour specificity, preservation of function and a good cosmetic result, side effects may cause treatment discontinuation in some cases. Treatment of EQ with PDT may represent a valuable option in selected cases, but our data do not allow considering it as a first-line therapeutic option.

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# Methylaminolaevulinic Acid Photodynamic Therapy in the Treatment of Erythroplasia of Queyrat

Laurence Feldmeyer Valérie Krausz-Enderlin Bettina Töndury Jürg Hafner  
Lars E. French Günther F.L. Hofbauer

Dermatology Department, University Hospital Zürich, Zürich, Switzerland

## Key Words

Erythroplasia of Queyrat · Photodynamic therapy ·  
Topical aminolaevulinic acid

## Abstract

**Background:** Erythroplasia of Queyrat (EQ) is an intra-epithelial carcinoma of the penis. Progression to invasive carcinoma may occur. Its cause is unknown but some evidence suggests infection with human papillomavirus in the pathogenesis of EQ; however, recent data do not confirm this. Therapy is difficult and associated with important recurrence rates. Photodynamic therapy (PDT) employs a photosensitizer excited by visible light. The resulting photodynamic reaction selectively destroys atypical cells. Only few reports exist on the use of topical PDT in the treatment of EQ. **Objective:** We report 11 cases of EQ treated by topical methylaminolaevulinic acid (MAL) PDT. **Results:** Out of 11 male patients with EQ treated by topical MAL-PDT, 3 achieved complete remission sustained for 24 and 51 months and 4 a partial remission sustained for 2–45 months with a follow-up period of 4–45 months (1 patient lost to follow-up); surprisingly, 2 of the 4 patients with partial remission presented a complete remission after 20 and 45 months of follow-up, respectively, without further therapy. Four patients showed progression of the disease. **Conclusion:** Whereas topical MAL-PDT offers the advantages of tumour specificity, preservation of function and a good cosmetic result, side effects

may cause treatment discontinuation in some cases. Treatment of EQ with PDT may represent a valuable option in selected cases, but our data do not allow considering it as a first-line therapeutic option. Copyright © 2011 S. Karger AG, Basel

## Introduction

Erythroplasia of Queyrat (EQ) was originally described by Tarnovsky in 1891. It was some 20 years later that the French dermatologist Queyrat carried out more detailed studies delineating this condition as a distinct entity [1]. EQ is an intra-epithelial carcinoma of the penis and represents an in-situ form of squamous cell carcinoma. Infection with oncogenic human papillomaviruses can be demonstrated in the great majority of cases [2], although a recent study cast doubt on this, showing absence of PCR-detectable human papillomavirus in EQ in 11 patients; further investigations are needed in order to confirm the role of human papillomavirus in delineating this risk [3]. Clinically, these lesions present as single or multiple, erythematous, sharply demarcated often velvety, shiny plaques. Progression to invasive squamous carcinoma may occur in up to 30% [2, 4]. Surgery is the gold standard therapy for EQ. Generally, a surgical approach is more reliable in terms of clinical and histological resolution, but as it is an invasive method, one should

**Table 1.** Details of the patients presenting with EQ

Pa-tient	Age at diag-nosis (years)	Previous treatment before PDT	Number of PDT sessions	Adverse events	Interval between treatments (weeks)	Primary clinical outcome after PDT	FDD primary outcome	Recurrence-free follow-up months after last PDT	Further treatment	Outcome
1	49	imiquimod, 5-fluorouracil, circumcision	11	none	1–48	complete remission	no specific enhancement	51	none	complete remission (51)
2	61	imiquimod, circumcision	7	erythema, dysuria	1–20	complete remission	no specific enhancement	24	none	complete remission (24)
3	65	none	19	redness, swelling, dysuria, haematoma	1–10	complete remission	n.d.	1.5	none	complete remission (h.c.) (1.5)
4	77	CO <sub>2</sub> laser, circumcision	16	none	1–6	partial remission	n.d.	2	radiotherapy	complete remission (4)
5	87	none	8	none	1–7	partial remission	stationary (isolated fluorescent macula)	n.d. (patient lost to follow-up)	n.d. (patient lost to follow-up)	n.d. (patient lost to follow-up)
6	70	none	5	after 5th treatment redness, swelling and pain of gland	1	partial remission	n.d.	20	none	complete remission (h.c.) (20)
7	71	imiquimod, circumcision	12	erythema, dysuria (once)	1–11	partial remission	no specific enhancement	45	none	complete remission (45)
8	83	none	2	painful inflammatory reaction	1	progression	n.d.	12	CO <sub>2</sub> laser	complete remission (16)
9	51	imiquimod	3	n.d.	n.d.	progression	n.d.	6	CO <sub>2</sub> laser	recurrence (12)
10	65	5-fluorouracil, imiquimod	2	n.d.	8	progression	n.d.	6	radiotherapy, CO <sub>2</sub> laser, circumcision	complete remission (17)
11	80	none	4	painful inflammatory reaction	2	progression	n.d.	0	radiotherapy	–

Figures in parentheses indicate months of total follow-up after last PDT. n.d. = Not determined; h.c. = histologically confirmed.

take into consideration cosmetic and functional demands. Mohs micrographic surgery is favoured because it precisely identifies tumour-free margins while sparing normal tissue, thus optimizing cosmetic and functional outcomes [5–7]. In our patients, photodynamic therapy (PDT) was chosen either because of a previous failure of topical therapy (imiquimod, 5-fluorouracil) or in case of recurrence after surgery, when the patient declined repeat surgery, as well as first-line therapy in 5 patients.

### Photodynamic Treatment Protocol of the Glans Penis

Methylaminolaevulinate 160 mg/g of vehicle (MAL) was applied for 3 h under an occlusive dressing to the glans penis covering the affected area as well as a 5-mm

margin of clinically normal surrounding tissue. Before illumination, a local anaesthetic penile ring block using 2% lidocaine without adrenalin was applied. The affected areas were then illuminated using a non-coherent red light source (Waldmann® PDT 1200L, 570–670 nm) with a total dose of 75 J/cm<sup>2</sup>. The therapeutic response was evaluated clinically at regular intervals as well as by fluorescence dynamic diagnosis (FDD) in a subgroup of patients.

### Case Reports

A total of 11 patients with EQ affecting the glans penis were treated by PDT. The patients' characteristics are summarized in table 1. In all cases the diagnosis was confirmed by histology before PDT. In some cases, the clinical follow-up was documented with photographs (fig. 1).



**Fig. 1.** Clinical pictures before (left) and after (right) PDT in patients No. 3, 5, 6 (partial remission) and 11 (progression).

All male patients were aged 49–87 years at diagnosis (mean 69 years). For 5 patients, PDT was the first-line treatment (patients No. 3, 5, 6, 8 and 11), while the other patients had already undergone treatment with topical imiquimod (patients 1, 2, 7, 9 and 10), topical 5-fluorouracil (patients 1 and 10), carbon dioxide laser (patient 4) or circumcision (patient 1, 2, 4 and 7). The patients underwent between 2 and 19 PDT treatment sessions (mean 8 sessions). The interval between 2 sessions varied from 1 to 48 weeks.

Out of 11 patients, 3 achieved a long-term complete response sustained for 24 and 51 months (patients 1–3), respectively, and 4 a partial remission (patients 4–7, clinically residual small red plaque) sustained for 2–45 months with a follow-up period of

**Table 2.** Treatment modalities for EQ as reported in the literature

Modality	Reference No.
PDT	8
Electrocautery and curettage	9
5-Fluorouracil cream	10
Imiquimod cream	11–14
Isotretinoin	15
Cryotherapy	16, 17
Laser ablation	18–21
Radiotherapy	22–24
Circumcision	5, 25
Local excision	5
Mohs surgery	5–7
Total glans resurfacing	26
Cidofovir	27

4–45 months (1 patient lost to follow-up). Histological confirmation of remission was obtained in 2 cases (patients 3 and 6). It is noteworthy that 2 of the 3 patients with complete remission had been resistant to previous treatments. Surprisingly, 2 of the 4 patients with partial remission after PDT (patients 6 and 7) presented a complete remission after 20 and 45 months of follow-up, respectively, without further therapy. Retrospectively, as no confirmation biopsy was performed immediately after the end of treatment in these patients, the redness interpreted as residual disease may have been only a side effect of therapy. Four patients showed a progression (patients 9 and 10) or did not tolerate the therapy (patients 8 and 11). Five patients required another therapeutic modality subsequently (patients 4 and 8–11). FDD was used in 4 patients (patients 1, 2, 5 and 7) and compared to the clinical evaluation of residual disease. FDD correlated only partly with the clinical assessment: in the 4 patients where FDD was performed, 3 showed a correlation with the clinical status whereas in patient 7, FDD showed no fluorescence while a red macula was clinically visible on his mucosa. In 2 cases (patients 3 and 6), a biopsy was performed just after, respectively, at a distance to the end of therapy because of a suspicion of recurrence: neither histology showed signs of malignant transformation. This suggests that the evaluation of the outcome is clinically difficult.

The mean number of PDT sessions was 12.3 in the complete response, 10.3 in the partial remission group, whereas it was only 2.8 in the progression group.

Most patients experienced erythema and mild to moderate burning at the site of application during illumination, followed by mild swelling. Reported adverse effects included discomfort associated with dysuria, which subsided over the following 1–3 days before it resolved completely (patients 2, 3, 6 and 7). Haematoma at the site of PDT was reported by patient No. 3. Patients 8 and 11 had to stop PDT because of adverse events: both had a very painful inflammatory reaction after 2 sessions. Three patients (No. 1, 4 and 5) reported no adverse events. No information on adverse events was available for 2 patients (No. 9 and 10).



## Discussion

The treatment options for EQ reported in the literature are numerous as listed in table 2. MAL-based PDT – depending on the country – is a registered treatment for superficial basal cell carcinoma, Bowen's disease and actinic keratosis and a reported treatment option for squamous cell carcinoma [28]. Topical MAL-PDT combines MAL, which is converted into protoporphyrin IX within cells, and visible light to produce a photodynamic effect in the presence of oxygen, resulting in the formation of cytotoxic reactive oxygen species. It leads to a selective destruction of abnormal cells while preserving normal cells and results in an excellent cosmetic outcome. PDT is a highly effective therapy for the treatment of Bowen's disease, a carcinoma in situ affecting the outer skin and similar in histology and presentation to EQ with complete remission in approximately 90% of patients treated and partial remission in 7.5% of patients treated [29, 30].

We present 11 patients with EQ who were treated by topical MAL-PDT. Of 11 patients, 3 achieved a complete response, 4 a partial remission, and 4 had a progression of disease. Whereas 5 patients required a subsequent therapeutic modality following MAL-PDT, PDT was a very satisfactory therapy for 5 other patients (1 patient lost to follow-up). Of note, the 4 patients who underwent circumcision before PDT seemingly showed a better outcome with 2 complete and 2 partial remissions. Others have reported on the use of PDT in EQ with similar results: Stables et al. [8] reported 4 patients with EQ treated by topical 5-aminolaevulinic acid PDT. Of 2 patients with limited disease, 1 achieved a long-term complete response (36 months) after a single cycle of treatment and the other remained free of disease for 18 months after the second treatment. Two further patients with more extensive disease achieved partial response after 2 cycles of 5-aminolaevulinic acid PDT and required laser vaporization [8]. Lee and Ryman [9] reported an 82-year-old patient with invasive squamous cell carcinoma of the glans penis arising in EQ. While he underwent Mohs micrographic surgery for his invasive carcinoma, his residual EQ was treated by PDT. Eighteen weeks after completion of one cycle of treatment, he had no evidence of recurrence [9].

Although the small number of reported cases (5 patients to date [8, 9]) does not allow a relevant statistical comparison of the success of this therapy, our results document a favourable outcome after PDT for some of the patients and underline the importance of repeated treatment. Indeed, the mean number of PDT sessions in our

patient collective was 12.3 in the complete response group, 10.3 in the partial remission group, whereas it was only 2.8 in the progression group. The patients of Stables et al. [8] had 1–2 cycles, that of Lee and Ryman [9] 1 cycle of therapy only. We think therefore that the success of the PDT therapy for EQ is closely linked to the number of sessions, and that patients treated by this method need to be regularly followed clinically. We believe that PDT provides a valuable option for selected cases like patients encountering recurrence after surgery, or in patients where conservative treatment is preferred to surgery. The main advantages of PDT are the good tolerability with limited adverse events in comparison to more invasive treatments [31] as well as the good cosmetic result. Nevertheless, side effects may cause treatment discontinuation in some cases. The main drawbacks are the high recurrence rate which mandates a regular clinical follow-up as well as the time-consuming treatment.

## Conclusion

There have only been few reports on 5-aminolaevulinic acid -PDT in the treatment of EQ. We provide here clinical data on MAL-PDT for EQ as a viable treatment for half of our 11 patients. However, complete remission immediately after therapy has been achieved in 3 patients only. Two of the 4 patients with partial remission after PDT presented a complete remission at the follow-up, without further therapy. The redness interpreted as residual disease may have been only a side effect of therapy. Four patients were non-responders, requiring further treatment.

Our results indicate that treatment of EQ with MAL-PDT may represent a valuable option in selected cases of histologically confirmed EQ, with preserved function and good cosmetic outcome. However, our data do not allow considering it as a first-line therapeutic recommendation. Data from the literature also report inconsistent success. In conclusion, PDT may have a favourable outcome for some patients with EQ, but long-term efficacy and safety should be assessed on a larger clinical basis. Long-term follow-up is important to recognize and treat relapses at an early time point.

## Disclosure Statement

The authors have no conflicts of interest.

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